REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity. The claims as presented are fully supported by the disclosure, including the claims as originally filed.

The Examiner objects to the specification on the basis that the documents incorporated into the specification by reference do not support H3 Lys 79 (Me) and its corresponding sequence. Respectfully, in considering the disclosure of the incorporated documents, the Examiner has not considered the disclosure of the subject specification itself.

The H3 Lys 79 (Me) mark is disclosed in the specification on page 6, line 1 and Tables 1 and 2. Since the H3 Lys 79 (Me) mark is disclosed in the specification itself, there is no requirement for it to be in the documents which are incorporated by reference. However, the amino acid sequence of histone H3 (i.e.m SEQ ID NO:11) is disclosed in the NHGRI/NCBI histone database which is cited on page 4, line 24 (and incorporated by reference at page 23, lines 17 and 18). The combination of NHGRI/NCBI histone database and the specification, therefore, provide basis for the H3 Lys 79 (Me) mark and the sequence of histone H3 (SEQ ID NO: 11).

The H3 sequence is also recited in figure 1c of Luger et al, which is also incorporated by reference at page 4, lines 20 and 21. Luger et al does not show methylation at lysine 79, however, the H3 Lys 79 (Me) mark is disclosed in the specification, as pointed out above. Luger provides basis for the sequence of histone H3. The combination of Luger et al and the specification, therefore, also provide basis for the H3 Lys 79 (Me) mark and the sequence of histone H3 (SEQ ID NO:11).

The H3 sequence is also recited in figure 1B of Ausio et al, also incorporated by reference at page 4, lines 22 and 23. Ausio et al does not show methylation at lysine 79, however, the H3 Lys 79 (Me) mark is disclosed in the specification. The combination of Ausio et al and the specification, therefore, also provide basis for both the H3 Lys 79 (Me) mark and the sequence of histone H3 (SEQ ID NO: 11).

In view of the above, it will be clear that the histone 3 sequence that was introduced via the Amendment filed December 7, 2009 is the material previously incorporated by reference. Further, it will be clear that the subject specification provides support for the H3 Lys 79 (Me) mark.

If the Examiner has any remaining concerns, she is urged to contact the undersigned by phone. Otherwise, withdrawal of the objection is requested.

Claims 1-3, 6-14, 20, 25-33, 35 and 44-48 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is in order for the reasons that follow.

The Examiner contends that neither Luger et al nor Ausio et al support the claimed feature of methylation of histone H3 at a lysine residue corresponding to Lysine 79 of SEQ ID NO:11. However, the disclosure of the specification includes both information which is explicitly recited and information which is incorporated by reference to other documents which fully support the claimed feature.

The instant claim 1 recites:

> *wherein the antibody binds specifically to histone H3 which is methylated at a lysine residue corresponding to lysine 79 of the histone H3 sequence of SEQ ID NO: 11 and does not bind to histone H3 which is not methylated at said lysine residue*

Support for the methylation of Lys 79 of histone H3 is provided at page 6, line 1 and Tables 1 and 2 of the specification. Support for the histone H3 sequence of SEQ ID NO: 11 is provided by the material which is incorporated into the specification by reference to any one of Luger et al, Ausio et al and the NHGRI/NCBI histone database. Taken as a whole, the specification, including the information which is incorporated by reference, provides support for the feature of the H3 Lys 79 (Me) mark.

Reconsideration of the rejection is therefore requested.

Claims 1-3, 6-14, 20, 25-33, 35 and 44-48 stand rejected under 35 USC 103 as allegedly being obvious over Allis *et al.* (US 2006/0073517) in view of Allis (b) (US 2005/0069931). Withdrawal of the rejection is submitted to be in order for the reasons that follow.

In rejecting the claims as obvious, the Examiner contends that one of ordinary skill in the art would have been motivated to diagnose disease using nucleosome and modified histone proteins with a reasonable expectation of success from the teachings in both Allis references that specific histone modifications serve as diagnostic markers of disease. Applicants respectfully disagree for the reasons that follow.

Claims 1-3, 6, 20, 25-33 and 35 relate to antibodies which bind exclusively to H4 Lys 16 (Ac) and H3 Lys 79 (Me).

Allis *et al.* makes reference to H3 Lys 79 (Me) and suggests that it may reduce suppressor binding. Allis *et al* also refers to the H4 Lys 16 acetyl-mark as the binding site for the bromodomain of Gen5 (see paragraph [0075]).

Allis *et al* is totally silent about any association between H4 Lys 16 (Ac) and/or H3 Lys 79 (Me) and disease, likewise, the association between disease and the identification of these marks in cell-free samples.

Allis (b) fails to remedy this deficiency and is totally silent about the association of between H4 Lys 16 (Ac) and/or H3 Lys 79 (Me) with any disease condition. In the absence of such teaching, one of ordinary skill in the art would have had no reasonable expectation of success in diagnosing disease through the detection of these markers on cell free nucleosomes.

Claims 1-3, 6, 20, 25-33 and 35 would, therefore, not have been obvious over Allis *et al.* in view of Allis (b).

Claims 7 to 14 relate to methods of assessing a disease that involve determining antibody binding to a histone modification in nucleosomes using a double-antibody format.

Neither Allis *et al* nor Allis (b) refers to a double antibody format in which one antibody binds specifically to the modified histone, while the other antibody binds to a nucleosome but does not bind to the modified histone.

Prior to the present invention, one of ordinary skill in the art could not have reasonably expected that a two-site immunoassay could be developed to successfully detect modified histones directly in biological samples.

Allis *et al* and Allis (b) suggest the development of an antibody which binds to the epitope containing the histone modification. However, they are both totally silent about the possibility of a two antibody immunoassay, and provide no teaching or suggestion regarding the second antibodies which could be used in such an immunoassay.

This would have presented a significant problem for one of ordinary skill in the art. If the second antibody bound to an epitope on the same histone as the modification, then there would be a significant risk of masking, such that the two antibodies would compete with each other for binding. This would prevent the operation of a two-site immunoassay.

Cell-free nucleosomes are degraded in blood. If the second antibody bound to an epitope in a different part of the nucleosome, then there would be a significant risk that the epitope for the second antibody would either be separated from the epitope containing the histone modification or would be absent altogether. This would also prevent the operation of a two-site immunoassay.

Neither Allis *et al.* nor Allis (b) provide any teaching that would suggested to one of ordinary skill in the art that cell-free nucleosomes in a biological sample would be a suitable target for a two-site immunoassay or that such an immunoassay would provide a sensitive and reproducible method for detecting modified histones and treating disease.

In the absence of such teaching, one of ordinary skill in the art would have had no reasonable expectation of success in diagnosing disease through a 2 site immunoassay for modified histones in cell free nucleosomes.

Claims 7-14 would, therefore, not have been obvious over Allis *et al.* in view of Allis (b).

Claims 44-48 relate to a method of determining the presence of a cell-free nucleosome having a histone modification which involves detecting the presence of an endogenous antibody which binds specifically to that particular histone modification.

Allis *et al.* and Allis (b) describe the use of antibodies to detect specific modified histones in samples. However, Allis *et al.* and Allis (b) are totally silent about the existence of endogenous antibodies which bind specifically to modified histones.

Modified histones are self-antigens which are present at very low concentrations in blood. In the light of this, and in the absence of any teaching about the immunogenicity of modified histones, there could have been no reasonable expectation that endogenous antibodies which bind specifically to modified histones might exist. One of ordinary skill in the art would,

therefore, have had no reasonable expectation of success in diagnosing disease by detecting a endogenous antibodies which bind specifically to modified histones.

Claims 44-48 would, therefore, not have been obvious over Allis *et al.* in view of Allis (b).

In view of the above, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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